All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at −01.00, −00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of −70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. **1-3**. With reference to FIG. **1**, method of fill material **100** is shown. Step **102** comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step **104** comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **102** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step **106** comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **106** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2.

Step **108** comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step **110** comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **110** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Step **112** comprises degasing. The resulting mixture from step **112** may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. **2**, softgel capsule, i.e. gel mass, production **200** is shown. Step **202** comprises mixing glycercin with water. The water used in step **202** may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **202** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Heating may be performed until the temperature reaches 80° C.±5° C.

Step **204** comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **204** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. A vacuum may be drawn in step **204** to de-aerate.

Step **206** comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step **206** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2. Step **208** comprises degasing. The resulting mixture from step **208** may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. **3**, softgel capsule assembly process **300** is shown. Step **302** comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/−3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step **304** comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step **208** of FIG. **2**. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/−10° C. The wedge temperature may be 38° C.+/−3° C. The drum cooling temperature may be 4° C.+/−2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step **304** thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step **306** comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step **308** may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step **310** may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises a C6-C12 oil.

2. The pharmaceutical formulation of claim **1**, further comprising partially solubilized progesterone.